
VEGF/neuropilin-2 regulation of Bmi-1 and consequent repression of IGF-1R define a novel mechanism of aggressive prostate cancer.

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Public Summary:

In summary, this study identifies NRP2 (Neuropilin 2) as a novel biomarker for predicting response to IGF-1R (insulin-like growth factor 1) therapy. A critical finding in this context is that NRP2 is a much more robust biomarker than the IGF-1R itself. This finding is significant because the IGF-1R, is also expressed normal glands, in contrast to NRP2. Importantly, the data presented provide a rationale for initiating clinical trials that combine inhibitors of both NRP2 and IGF-1R.

Scientific Abstract:

We show that the VEGF receptor neuropilin-2 (NRP2) is associated with high-grade, PTEN-null prostate cancer and that its expression in tumor cells is induced by PTEN loss as a consequence of c-Jun activation. VEGF/NRP2 signaling represses insulin-like growth factor-1 receptor (IGF-1R) expression and signaling, and the mechanism involves Bmi-1-mediated transcriptional repression of the IGF-1R. This mechanism has significant functional and therapeutic implications that were evaluated. IGF-1R expression positively correlates with PTEN and inversely correlates with NRP2 in prostate tumors. NRP2 is a robust biomarker for predicting response to IGF-1R therapy because prostate carcinomas that express NRP2 exhibit low levels of IGF-1R. Conversely, targeting NRP2 is only modestly effective because NRP2 inhibition induces compensatory IGF-1R signaling. Inhibition of both NRP2 and IGF-1R, however, completely blocks tumor growth in vivo.

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